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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Imazamox - 129171**: Health Effects Division Risk Characterization for Use of the New Chemical Imazamox in/on Soybeans (6F4649).

PRATS Case Number: 287237
PRATS DP Barcode numbers: D222186

FROM: Barbara Madden, Chemical Manager
Registration Section
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THROUGH: Michael Metzger, Chief
Risk Characterization and Analysis Branch
Health Effects Division (7509C)
and
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Health Effects Division (7509C)

TO: Edward Allen/Jim Tompkins PM Team 25
Fungicide Herbicide Branch
Registration Division (7505C)

The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate toxicology and residue chemistry data and conduct dietary, occupational, and residential risk assessments, as needed to estimate the risk to human health that will result from the use of the new chemical imazamox in/on soybeans.

A summary of the findings and an assessment of human risk resulting from the proposed use of imazamox are provided in this document. The hazard assessment was provided by Myron S. Ottley, Ph.D. of Toxicology Branch I; the product and residue chemistry data review by R.W. Cook of Chemistry Branch 1 - Tolerance Support; the dietary risk assessment by Brian Steinwand of the Science Analysis Branch; the occupational exposure by George Tompkins, Ph.D. of the Occupational and Residential Exposure Branch and the drinking water exposure assessment by Elizabeth Resek of the Environmental Fate and Effects Division.

I. EXECUTIVE SUMMARY

HED has reviewed toxicology and residue chemistry data submitted by the American Cyanamid Company in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and 40 CFR §158, to support pending registrations containing the new active ingredient (ai) imazamox. Technical imazamox, a free acid is to be formulated into two end-use products, a liquid formulation containing 12.1% ai as an ammonium salt and water soluble packets with 70% ai as a free acid for use as a herbicide in/on soybeans. The subchronic, chronic, carcinogenicity, developmental, and reproductive toxicity, mutagenicity and metabolism studies were conducted using technical imazamox, a free acid. HED has concluded that following absorption, the anion of the free acid and the ammonium salt would be toxicology indistinguishable.

The HED RfD/Peer Review Committee considered the No Observed Effect Level (NOEL) from the developmental toxicity study (MRID 43876216) in rabbits of 300 mg/kg/day to be the appropriate end-point for establishing the reference dose (RfD) for imazamox. An Uncertainty Factor (UF) of 100 was applied to account for both interspecies extrapolation and intraspecies variability. The toxicology data provided no indication of increased sensitivity of fetal animals to *in utero* exposure to imazamox. Therefore, an additional safety factor for the protection of sensitive subpopulations is not warranted. On this basis, the RfD was calculated to be 3.0 mg/kg/day.

The HED RfD/Peer Review Committee considered the carcinogenicity phase of the combined chronic toxicity/carcinogenicity study in rats (MRID 43891001) to be acceptable. The highest dose level tested, 20,000 ppm (1068 and 1284 mg/kg/day in males and females, respectively) is considered a limit dose. There was no significant increase in tumors of any type. The Committee also considered the carcinogenicity study in mice (MRID 43876215) to be acceptable. The highest dose level tested, 7000 ppm (1053 and 1348 mg/kg/day in males and females, respectively) is considered a limit dose. There was no significant increase in tumors of any type. The Committee determined that the treatment did not alter the spontaneous tumor profile in rats and mice. Therefore, the Committee concluded that the chemical is "Not Likely" to induce tumors in humans.

On February 11, 1997, the Toxicology Endpoint Selection (TES) Committee met to evaluate the existing toxicology database for imazamox and to assess appropriate toxicology endpoints and dose levels of concern that should be used for risk assessment purposes. No appropriate toxicological endpoints were identified for acute dietary exposure; short term, intermediate term, or chronic term occupational or residential exposure and inhalation

exposure. Therefore, risk assessments for any of these exposure scenarios are not required. Therefore, there are no chronic residential risk assessments to aggregate with the chronic dietary (food and drinking water) risk assessment.

A tolerance of 0.1 ppm in/on soybeans is recommended for dietary risk assessments. Based upon information provided in the metabolism studies and comparison to the maximum dietary burden there is no reasonable expectation of residues in meat, milk, poultry or eggs. Data in the soybean metabolism study indicate that residues of imazamox do not concentrate in soybean oil.

A chronic dietary risk assessment is required for imazamox. The chronic analysis for food showed that exposure from the proposed tolerance, for use of imazamox in/on soybeans, for the U.S. population and all 22 subgroups would be less than 1% of the RfD. The chronic analysis for drinking water showed that chronic exposure from drinking water to both the U.S. population and children would be less than 1% of the RfD. Therefore, the combined chronic dietary (food and drinking water) exposure to imazamox would be no greater than 1% of the RfD for both the U.S. population and children.

The drinking water values were developed for use in eco-risk assessment and represent a reasonable upper-bound estimate for eco-risk assessment. It is expected they represent an overestimate for human health risk. The chronic dietary analysis is also an upper-bound estimate of dietary exposure with all residues at tolerance level and 100 percent of the commodity assumed to be treated with imazamox. Therefore, even without refinements, HED does not consider the combined aggregate chronic dietary/drinking water risk to exceed HED's level of concern.

The residue chemistry and toxicological database are adequate to support a conditional registration for the use of imazamox in/on soybeans in terms of human health risk. The registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether imazamox share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for imazamox need to be modified or revoked.

II. BACKGROUND

American Cyanamid Company has proposed a permanent tolerance for residues of the new chemical imazamox from use on soybean seed at 0.1 ppm. Imazamox is a member of the imidazolinone class of herbicides. Technical imazamox, a free acid (EPA File Symbol 241-GTI) is to be formulated into two end-use products, a liquid formulation containing 12.1% ai as an ammonium salt (EPA File

Symbol 241-GTO) and water soluble packets with 70% ai as a free acid (EPA File Symbol 241-GIN).

The proposed Use Directions allow for an early postemergence (prebloom) application once per year to soybeans at 5 ounces/Acre (A) for the liquid formulation and 0.91 ounces/A for the water soluble packets [0.039 lb acid equivalent (ae)/A] with a non-ionic surfactant (1 qt/100 gal) or crop oil concentrate (1.5-2 pt/A) and liquid fertilizer solution (1-2 qt/A) or spray grade ammonium sulfate (2.5 lb/A). All applications require the addition of an adjuvant and a liquid fertilizer. Ground or aerial applications are permitted in minimum water spray volumes of 10 gal/A and 5 gal/A, respectively. Use directions include an 85-day PHI between application and harvest of soybean seeds. 5 ounces/Acre for the liquid formulation and 0.91 ounces/Acre for the water soluble packets with a non-ionic surfactant (1 qt/100 gal) or crop oil concentrate (1.5-2 pt/A) and liquid fertilizer solution (1-2 qt/A) or spray grade ammonium sulfate (2.5 lb/A). All applications require the addition of an adjuvant and a liquid fertilizer. Ground or aerial applications are permitted in minimum water spray volumes of 10 gal/A and 5 gal/A, respectively. Use directions include an 85-day PHI between application and harvest of soybean seeds.

III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

Chemical Name: (±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-methoxymethyl-3-pyridinecarboxylic acid

Common Name: Imazamox

PC Code Number: 129171

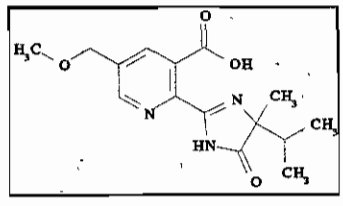
Empirical Formula: $C_{15}H_{19}N_3O_4$

Molecular Weight: 305.3

CAS Registry No.: 114311-32-9

Synonymous Names: AC 299,263 or CL 299,263

Structural Formula:



Physical and Chemical Properties of Imazamox - 97% Technical Grade Active Ingredient (TGAI) - MRIDs 43193201 through 43193203	
Color	off-white
Physical state	powdered solid
Odor	odorless
Melting point	166.0-166.7 C
Density, bulk density, or specific gravity	0.423 g/mL tapped bulk density at 24.5 C 0.304 g/mL untapped bulk density at 24.5 C
Solubility	Solvent — Solubility at 25 C deionized water (20 C) — 4413 ppm pH 5 buffer — 114,000 ppm pH 7 buffer — >643,000 ppm pH 9 buffer — >652,000 ppm hexane — 0.0006 g/100 ml methanol — 6.68 g/100 ml acetonitrile — 1.85 g/100 ml toluene — 0.21 g/100 ml acetone — 2.93 g/100 ml dichloromethane — 14.3 g/100 ml ethyl acetate — 1.02 g/ 100 ml
Vapor pressure	$<1.0 \times 10^{-7}$ torr at 25 C
Dissociation constant	2.3 and 3.3 at low to medium pH (0.5-6) and 10.8 at high pH (9-13) (TGAI; 98.2%)
Octanol/water partition coefficient	K_{ow} = 5.36 at pH 5 and 6 and 25 C
pH	2.35; 1% aqueous suspension (w:v) at 24.5 C
Stability	stable for at least 6 months at 25 C and 37 C; stable for one month at 45 C (after 3 months ai content decreased from 97.3% to 96.7%)
Oxidizing or reducing	no significant change in temperature, evolution of gases, noxious fumes, flames, or splattering observed on exposure to tap water, aqueous monoammonium phosphate (1% w:v), and 0.01 M aqueous potassium permanganate for up to 24 hours; after 24 hours, potassium permanganate changed from purple to brown; 1.4 mm/yr average corrosion rate calculated for zinc foil on exposure to an aqueous suspension for 14 days (MP)
Explodability	no impact sensitivity to 2 kg/100 cm impact energy at room temperature; one exotherm (heat release of -88 kJ/kg) on differential thermal analysis (DTA) between 20 and 300 C with an onset temperature of 180 C; determined to be a Class 1 dust with a characteristic dust constant Kst of 174 bar-m/sec; maximum explosive pressure was 6.3 bar, maximum pressure rise was 640 bar/sec
Storage stability	no significant decomposition or change in appearance after 9 months storage at ambient temperature in commercial packaging of polyethylene-lined cardboard (interim report)
Corrosion characteristics	no change in appearance of polyethylene bag or lined cardboard container following storage of the product for 9 months at ambient temperature (interim report)

B. Human Risk Assessment

1. HAZARD ASSESSMENT

Technical imazamox, a free acid is to be formulated into two end-use products, a liquid formulation containing 12.1% ai as an ammonium salt and water soluble packets with 70% ai as a free acid. The subchronic, chronic, carcinogenicity, developmental, and reproductive toxicity, mutagenicity and metabolism studies were conducted using technical imazamox, a free acid. HED has concluded that following absorption, the anion of the free acid and the ammonium salt would be toxicology indistinguishable. Therefore, the toxicology data discussed below can support the ammonium salt as well the free acid.

a. Acute Toxicity

Study Type	MRID	Results	Toxicity Category
Acute Oral - rat	43193207	LD_{50}= >5000 mg/kg	IV
Acute Dermal - rat	43193208	LD_{50}= >4000 mg/kg	III
Acute Inhalation - rat	43193209	LC_{50} >6.3 mg/L	IV
Primary Eye Irritation - rabbit	43193210	Moderate irritant	III
Primary Skin Irritation - rabbit	43193211	Non-irritating	IV
Dermal Sensitization - guinea pig	43193212	Non-sensitizer	

b. Subchronic Toxicity

The data base for subchronic toxicity is considered complete. No additional subchronic toxicity studies are required at this time.

i. Subchronic Oral Toxicity in Rats

In a subchronic oral toxicity study (MRID 43193219), rats were fed diets containing imazamox technical at 0, 1000, 10,000, or 20,000 ppm for 13 weeks. These doses correlated to 0, ~~81~~, 833 or 1661 mg/kg/day, respectively. No mortality, abnormal clinical signs or ophthalmological findings were related to treatment. Mean body weights, body weight gains and food consumption for all treatment groups were comparable to or greater than the control group. There were no effects on hematology, clinical chemistry or urinalyses parameters. There were no differences between absolute organ weight or organ weights relative to body weights of treatment and control group. No gross or microscopic pathology observations were related to treatment. Under the conditions of this study, a Lowest Observed Effect Level (LOEL) was not established. The NOEL was 1661

mg/kg/day (20,000 ppm), the highest dose tested (HDT).

ii. Subchronic Oral Toxicity in Dogs

In a subchronic toxicity study (MRID 43193220), dogs were fed diets containing imazamox technical at 0, 1000, 10,000 or 40,000 ppm for 13 weeks. These doses correspond to 0, 34, 329 or 1333 mg/kg/day for males and 0, 36, 381 or 1403 for females, respectively. There were no mortalities, abnormal clinical signs of toxicity or ophthalmological observations and no adverse effects on body weight, body weight gain or food consumption in either sex at any dose level. No treatment-related effects were observed in hematology, clinical chemistry or urinalyses parameters in either sex at any dose level. Organ weights, and gross and histopathology showed no treatment-related effects at any dose level. Under the conditions of this study, a LOEL was not established. The NOEL is 1.3 g/kg/day for males and 1.4 g/kg/day for females (40,000 ppm), HDT.

iii. Twenty-eight Day Dermal Toxicity Study in Rats

In a repeated dose dermal toxicity study (MRID 43876213), imazamox technical was applied to the shaved skin of rats at dose levels of 0, 250, 500, or 1000 mg/kg for 6 hours/day, 5 days/week, for 4 weeks. Imazamox had no observed toxic effect on the rats in this study. For all treatment groups, there were no clinical signs of toxicity, and body weights, body weight gains, and food consumption were similar to the controls. There were no differences in ophthalmology, hematology parameters, clinical blood chemistry, organ weights, or macroscopic or microscopic organ morphology between rats in the treated and the control groups. No neoplastic tissue was observed. Urinalysis was not performed. No LOEL was established in this study. The NOEL was 1000 mg/kg, HDT.

c. Chronic Toxicity and Carcinogenicity

The data base for chronic toxicity and carcinogenicity are considered complete. No additional studies are required at this time.

i. Chronic Oral Toxicity Study in Dogs

In a chronic toxicity study (MRID 43876214), imazamox technical was administered to dogs in the diet at dose levels of 0, 1,000, 10,000, or 40,000 ppm (equivalent to the limit dose) for 1 year (approximately 0, 29.5, 282.5 or 1165 mg/kg/day, respectively). No mortality was observed during the study, and no treatment-related differences were observed for appearance, body weights, food consumption, ophthalmology, hematology, blood chemistry, urinalysis, organ weights, and gross and microscopic pathology. A LOEL was not established in this study. The NOEL

is approximately 1,165 mg/kg/day (40,000 ppm), HDT.

ii. Chronic Toxicity/Carcinogenicity Study in Rats

In a combined chronic/oncogenicity study (MRID 43891001), imazamox technical was administered to rats in the diet at dose levels of 0, 1,000, 10,000, or 20,000 ppm (equivalent to 0, 52, 528, or 1,068 mg/kg/day in males and 0, 63, 626, or 1,284 mg/kg/day in females) for 24 months. Mortality, body weights, body weight gains, feed consumption and feed efficiency of dosed animals were unaffected by treatment. No overt clinical signs of toxicity or ophthalmological changes were observed during the study and all hematological, blood chemistry, and urological parameters were unaffected by treatment. At necropsy, absolute and relative kidney weights in the 10,000 ppm group males were increased compared to concurrent controls, but no corroborative macroscopic or histopathological changes were detected in the kidneys. In addition, this was not a dose-related finding. There were no treatment related neoplastic lesions detected in rats treated with imazamox in the diet for 24 months. A chronic LOEL was not observed, however, the dose level of 20,000 ppm in the diet is considered an adequate upper limit for chronic and carcinogenicity studies. The chronic NOEL is equivalent to 1,068 mg/kg/day in males and 1,284 mg/kg/day in females (20,000 ppm), HDT.

iii. Carcinogenicity Study in Mice

In a mouse carcinogenicity study (MRID 43876215), imazamox technical was administered to mice in the diet at levels of 0, 500, 3,500, or 7,000 ppm (0, 73, 535, or 1,053 mg/kg/day for males and 0, 96, 664, or 1,348 mg/kg/day for females) for approximately 78 weeks. No treatment-related differences in clinical signs of toxicity, mortality, mean body weights, mean body weight gains, feed consumption, or feed efficiency were observed between control and treatment groups during the study. No statistically-significant differences were observed in hematology parameters, absolute organ weights, or relative organ/body weights for mice in the treated and control groups. No treatment-related gross postmortem or histological differences were seen for mice in the treated and the control groups. A LOEL was not established in this study. The NOEL is 1,053 mg/kg/day for males and 1,348 mg/kg/day for females (7,000 ppm), HDT.

d. Developmental Toxicity

The data base for developmental toxicity is considered complete. No additional studies are required at this time.

i. Developmental Toxicity in Rats

In a developmental toxicity study (MRID 43193221), imazamox

was administered to pregnant rats by oral gavage at dose levels of 0, 100, 500 or 1000 mg/kg/day (Limit-Dose) during days 6 through 15 of gestation. No maternal mortality or clinical signs of toxicity were seen. Mean body weights at 1000 mg/kg/day tended to be reduced during Days 8 to 20, but the decreases were not statistically significant. Mean body weight gain was statistically significantly reduced during the early dosing period (Days 6-12) at the 1000 mg/kg/day group compared to controls. However, body weight gains were comparable between the treated and the control group for the remainder of the dosage period (Days 12 -16) and the post dosage period (Days 16 -20). Absolute and relative feed consumption values tended to be reduced at 1000 mg/kg/day during the dosage and the post dosage periods; however, none of these differences showed statistical significance when compared to control values. Treatment had no effect on any of the cesarean parameters. The Maternal Toxicity LOEL is 1000 mg/kg/day based on the body weight effects. The Maternal Toxicity NOEL is 500 mg/kg/day. No treatment-related fetal gross external, visceral or skeletal malformations or variations were seen at any dose level. Therefore, a Developmental Toxicity LOEL was not established. The Developmental Toxicity NOEL is equal to or greater than 1000 mg/kg/day (Limit-Dose).

ii. Developmental Toxicity Study in Rabbits

In a developmental toxicity study (MRID 43876216), imazamox technical was administered to rabbits by oral gavage in 0.5% carboxymethylcellulose at dose levels of 0, 300, 600, or 900 mg/kg/day from days 7 through 19 of gestation. Maternal toxicity was demonstrated at 600 mg/kg/day by reduced food consumption during treatment. Reduced food consumption during treatment was also noted in the 900 mg/kg/day group rabbits, as well as reduced body weight gains. There were no treatment-related effects on mortality, clinical signs of toxicity, or cesarean parameters at any dose level. The Maternal Toxicity LOEL was 600 mg/kg/day, based on reduced body weights and food consumption in F1 males and females. The Maternal Toxicity NOEL was 300 mg/kg/day. There were no treatment-related effects in developmental parameters. A developmental LOEL was not observed. The developmental NOEL equal to or greater than 900 mg/kg/day, HDT.

e. Reproductive Toxicity

The data base for reproductive toxicity is considered complete. No additional studies are required at this time.

i. Reproductive Toxicity Study in Rats

In a 2-generation reproduction study (MRID 43876217), imazamox technical was administered to rats in the diet at dose levels of 0, 1,000, 10,000, or the limit dose 20,000 ppm

(equivalent to 0, 73-88, 748-892, or 1469-1826 mg/kg/day). Exposure to P animals began at 6 weeks of age and lasted for 10 weeks prior to mating to produce F1 pups. At 28 days of age, F1 pups were selected to become the parents of the F2 generation and were given the same concentration test diets as their dam. F1 animals were given test diets for 11 weeks prior to mating. There were no compound-related effects in the main categories of systemic or reproductive toxicity evaluated at any of the administered dose levels including the 20000 ppm limit dose. A LOEL was not established. The NOEL is the limit dose, 1705 mg/kg/day in females and 1469 mg/kg/day in males (20,000 ppm).

f. Mutagenicity

The data base, using the new Mutagenicity Initial Testing Battery guidelines is considered adequate. Based on the available mutagenicity studies, there are no concerns for mutagenicity at this time.

i. Gene Mutations

Salmonella typhimurium/Escherichia coli reverse gene mutation assay (MRID 43193222): Independently performed tests were negative in S.typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 and E.coli strain WP2 uvrA$^-$ up to the highest dose tested (5000 µg/plate +/- S9).

Chinese hamster ovary (CHO) cells HGPRT forward gene mutation assay (MRID 43193223): Independently performed tests were negative up to the solubility limit of the test substance (4000 µg/mL +/-S9).

ii. Chromosome Aberrations

In vitro cytogenetic assay in Chinese hamster ovary (CHO) cells (MRID 43193225). The test was negative up to a dose near or at the solubility limit (3333 µg/mL +/-S9).

Mouse micronucleus assay (MRID 43193224): The test was negative in male or female CD-1 mice up to the highest administered oral gavage dose (5000 mg/kg). No definitive evidence of an overt toxic response in the treated animals or a cytotoxic effect on the target cells was observed.

No mutagenicity information was available in the open literature (GeneTox data base, published studies). The negative mutagenicity studies do, however, support the lack of an oncogenic effect in the rat and mouse long-term feeding studies and also the absence of significant reproductive or developmental toxicity attributable to a mutagenic mode of action (i.e., decreased total implants, increased resorptions).

g. Metabolism

The data base for metabolism is considered to be complete. No additional studies are required at this time.

i. Metabolism Study in Rats

In a rat metabolism study (MRID 43876218), [pyridine-6-^{14}C]imazamox was administered to rats as a single intravenous dose at 10 mg/kg body weight or orally by gavage as a single dose at 10 or 1,000 mg/kg or as a single oral dose at 10 mg/kg following a 14-day pretreatment with unlabeled imazamox at 10 mg/kg. [^{14}C]Imazamox was readily absorbed by male and female rats following intravenous or oral dosing. Greater than 73% of the administered dose was excreted in the urine within 24 hours of dosing. Pretreatment and dose level had little effect on the proportion of dose eliminated in urine from the oral dose groups. The rate of urinary excretion for the low and high oral dose groups was lower than the intravenous groups, suggesting a lack of complete absorption of the test substance. Within 168 hours of dosing at 10 mg/kg (with or without pretreatment) or 1,000 mg/kg, 88.0 to 99.3% of the administered dose was recovered from both sexes, of which 74.0 to 91.2% was in the urine. Fecal excretion comprised 1.9 to 2.7% of the administered dose in the intravenous groups, compared to 12.2 to 24.2% in all oral dose groups. Organic volatiles were not expected to form (not measured). Total [^{14}C]imazamox equivalents in tissues accounted for less than or equal to 0.007% of the actual administered dose for all treatment groups.

High performance liquid chromatography/Mass spectrometry (HPLC/MS) analyses of 0-6 hour urine extracts from the high dose males and females identified unchanged imazamox (98% of the recovered activity) in both sexes, and two minor metabolites, 5-(hydroxymethyl)-2-(4-isopropyl-4-methyl-5-oxo-2-imazazolin-2-yl)nicotinic acid (CL 263,284; 1%), and 2-(4-isopropyl-4-methyl-5-oxo-2-imadazolin-2-yl)-3,5-pyridine-dicarboxylic acid (CL 312,622; 0.2-0.3%). In addition, a trace amount of the activity was identified as the methyl ester of CL 299,263 (CL 303,190). HPLC/MS analyses of the feces extracts from male rats isolated imazamox (73% of the recovered activity), CL 263,284 (9%), and CL 312,622 (3%). In addition, a trace amount of the activity was identified as N-methyl CL 299,263.

The primary imazamox metabolic pathway in rats is initiated by cleavage of the methoxy-moiety on the parent molecule to form the alcohol metabolite, CL 263,284, which is then oxidized to form the di-acid metabolite, CL 312,622.

2. DOSE RESPONSE ASSESSMENT

a. Reference Dose and Safety Considerations for Infants and Children Under FQPA

The RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. The RfD is determined by using the toxicological end-point of the NOEL for the most sensitive mammalian toxicological study. The HED RfD/Peer Review Committee met on February 11, 1997 to evaluate the existing toxicology database for imazamox, discussed in the HAZARD ASSESSMENT section above, and to assess the RfD for imazamox.

The HED RfD/Peer Review Committee recommended that a RfD for imazamox be established based on the developmental toxicity study (MRID 43876216) in rabbits. The study has a Maternal Toxicity LOEL of 600 mg/kg/day, based on reduced body weights and food consumption in F1 males and females. The Maternal Toxicity NOEL is 300 mg/kg/day. An Uncertainty Factor (UF) of 100 was applied to account for both interspecies extrapolation and intraspecies variability.

The Food Quality Protection Act (FQPA), recently enacted as an amendment to FIFRA, requires that pesticide regulatory review incorporate an assessment of potential hazards to infants and children and include additional safety factors, of up to 10 fold when warranted, for the protection of these sensitive subpopulations. The toxicology data for imazamox includes an acceptable two-generation reproduction study (MRID 43876217) in rats and acceptable prenatal developmental toxicity studies in rats (MRID 43193221) and rabbits (MRID 43876216). In the two-generation reproduction study in rats, no evidence of toxicity was noted in either the adults or the offspring at dietary levels that exceeded the limit dose. In the prenatal developmental toxicity study in rats, no developmental toxicity was observed up to and including the highest concentration tested (1000 mg/kg/day). Maternal systemic toxicity at that dose level consisted of decreased body weight gain during the treatment period. In the prenatal developmental toxicity study in rabbits, no evidence of developmental toxicity was observed up to the HDT of 900 mg/kg/day, while maternal toxicity (reduced food consumption during the treatment period) was noted at 600 mg/kg/day (maternal NOEL = 300 mg/kg/day).

The HED RfD/Peer Review Committee concluded that the toxicology data provided no indication of increased sensitivity of fetal animals to *in utero* exposure to imazamox. Therefore, an additional safety factor for the protection of sensitive subpopulations is not warranted.

On this basis, the RfD was calculated to be 3.0 mg/kg/day.

It should be noted that this chemical has not been reviewed by the FAO/WHO joint committee meeting on pesticide residue (JMPR) and that an acceptable daily intake (ADI) has not been established by that Committee.

b. Carcinogenicity Classification and Risk Quantification

The HED RfD/Peer Review Committee considered the carcinogenicity phase of the combined chronic toxicity/carcinogenicity study in rats (MRID 43891001) to be acceptable. The highest dose level tested, 20,000 ppm (1068 and 1284 mg/kg/day in males and females, respectively) is considered a limit dose. There was no significant increase in tumors of any type. The Committee also considered the carcinogenicity study in mice (MRID 43876215) to be acceptable. The highest dose level tested, 7000 ppm (1053 and 1348 mg/kg/day in males and females, respectively) is considered a limit dose. There was no significant increase in tumors of any type.

The Committee determined that the treatment did not alter the spontaneous tumor profile in rats and mice. Therefore, the Committee concluded that the chemical is "Not Likely" to induce tumors in humans.

c. Toxicological Endpoints for Risk Assessment

On February 11, 1997, the Toxicology Endpoint Selection (TES) Committee met to evaluate the existing toxicology database for imazamox, discussed in the HAZARD ASSESSMENT section above, and to assess appropriate toxicology endpoints and dose levels of concern that should be used for risk assessments purposes for the following exposure scenarios: acute dietary (one day), short term dermal occupational or residential (1 to 7 days), intermediate term dermal occupational or residential (1 week to several months), chronic dermal occupational or residential (several months to lifetime), and inhalation (any time period).

No appropriate endpoints were identified for any of these exposure scenarios. Therefore, acute dietary, short term, intermediate term, chronic term, and inhalation risk assessments are not required.

No dermal absorption data are available. Dermal absorption is not a concern at this time since no appropriate endpoints were identified for any of the exposure scenarios via the oral route. However, if exposure becomes a concern in the future, a dermal absorption rate of 100% should be assumed, due to lack of appropriate data.

3. DIETARY EXPOSURE AND RISK CHARACTERIZATION

a. Dietary Exposure - Food Sources

i. Plant Metabolism

American Cyanamid submitted a soybean metabolism study (MRID 43193234) depicting the metabolism of [6-pyridine-^{14}C]imazamox in soybeans. Field-grown soybeans were treated with a single preplant incorporated (PPI) application of [6-pyridine-^{14}C]imazamox at 0.130 lb acid equivalent (ae)/A (3.3x the proposed maximum single application rate) or a single postemergence application at 0.134 lb ae/A (3.4x), the petitioner characterized/identified 84.3-93.7% of total radioactive residues (TRR) in soybean forage and straw. Imazamox represented the single identified component in soybean forage collected 0 days following the postemergence application, but was a minor component in samples of forage and straw collected at later intervals following treatment: 3.0% of TRR (<0.01 ppm) in 28-DAT soybean forage from the PPI application and 1.5% and 17% of TRR (<0.01 ppm) in soybean forage collected 30-DAT and straw collected 123-DAT, respectively, from the postemergence application. CL 189,215 represented the major identified metabolite in soybean matrices; 33.1% of TRR (0.04 ppm) in 28-DAT forage from the PPI application, and 24.2% and 11.1% of TRR (0.02 ppm and 0.01 ppm) in 30-DAT soybean forage and 123-DAT soybean straw, respectively, from the postemergence application. Two other metabolites, CL 263,284 and CL 312,622 were also identified at levels higher than the active ingredient in 28-DAT forage from the PPI application and 30-DAT soybean forage and 123-DAT soybean straw from the postemergence application. The petitioner has not proposed a PPI use for imazamox.

For establishment of a permanent tolerance in/on soybeans, the nature of the residue in soybeans is adequately understood.

ii. Animal Metabolism

Goats

American Cyanamid submitted data (MRID 43193235) depicting the metabolism of [6-pyridine-^{14}C]imazamox in lactating goats. Two dose levels were prepared by diluting [6-pyridine-^{14}C]imazamox (specific activity 80.6 μCi/mg, radiochemical purity 98.0%; and specific activity 78.2 μCi/mg, radiochemical purity 97.7%) with unlabeled imazamox to final specific activities of 8.98 μCi/mg and 13.3 μCi/mg for the low- and high-dose treatments, respectively. The test substance was administered orally by gelatin capsule for 7 days to one lactating goat at a low dose equivalent to a 2.08-ppm feeding level and to one lactating goat at a high dose equivalent to an 11.6-ppm feeding level. The data indicate that radioactivity was not quantifiable

(<0.01 ppm) in all samples of milk and tissues (liver, loin and leg muscle, and omental fat) except the kidney of low- and high-dose goats. Respective ^{14}C-residues of 0.02 ppm and 0.06 ppm were detected in kidney samples from the low- and high-dose goats. The excreta contained 106% and 89% of the administered radioactivity in the low- and high- dose goat, respectively, primarily in urine. Of the excreted ^{14}C, urine accounted for 91% - 65% and feces 15% - 24% (low- and high-dose goat, respectively). The ^{14}C in high-dose urine was analyzed by reverse phase HPLC and showed that greater than 91% of the ^{14}C was imazamox.

The ^{14}C in the kidney is likely to have been eliminated in subsequent urination. Considering the exaggeration of the dosage levels (93x and 516x the maximum theoretical dietary burden based on a diet containing 20% soybean seed), the identification of majority of the residue in urine as imazamox, and the calculated dietary burden (0.017 - 0.025 ppm), detectable residues of imazamox would not be expected in kidney tissue.

Poultry

American Cyanamid submitted data (MRID 43193236) depicting the metabolism of [6-pyridine-^{14}C]imazamox in laying hens. Two dose levels were prepared by diluting [6-pyridine-^{14}C]imazamox (specific activity 80.6 μCi/mg, radiochemical purity 96.3%) with [^{13}C]imazamox (as a mass marker) and unlabeled imazamox to a final specific activity of 10.8 μCi/mg. The test substance was administered orally by gelatin capsule for 7 days to eight white Leghorn laying hens at a low dose equivalent to a 2.11-ppm feeding level and to eight hens at a high dose equivalent to a 10.2-ppm feeding level. The majority of the administered radioactivity (ca. 85%) was eliminated in the excreta of hens from both the low- and high-dose groups. These data are adequate for the purposes of establishing a permanent tolerance for imazamox on soybeans. Based on the available data, there is no reasonable expectation of finite imazamox residues occurring in poultry tissues or eggs as a result of feeding soybean seed containing residues at the proposed tolerance level; thus, no poultry feeding studies or secondary tolerances for animal commodities are required.

iii. Residue Analytical Method - Plants

American Cyanamid submitted method descriptions and validation data (MRID 43193237) for an HPLC/ultraviolet light (UV) method (Method M 2248) for determining residues of imazamox in/on soybean seed. Concurrent recovery data (MRID 43193239) were submitted with the soybean seed field residue studies. A method description and supporting validation data were also submitted for a confirmatory HPLC/MS method (Method M 2333).

M 2248: Samples of soybean seed are extracted with 1 N HCl:water:methanol (1:39:60, v:v:v), sonicated, and vacuum filtered. The filter cake is washed with the extracting solvent, and the filtrates are combined. An aliquot of the filtrate is concentrated by rotary evaporation, and the pH of the concentrated aqueous solution is adjusted to 2.5 with 1 N HCl. The aqueous solution is then partitioned four times with methylene chloride. The methylene chloride phases are collected, combined, rotary evaporated almost to dryness, redissolved in ethyl acetate, and cleaned up by gel permeation chromatography (GPC) using a glass column packed with Bio-Rad Bio-Beads and ethyl acetate as the eluting solvent. The eluate is collected, rotary evaporated to dryness at 40 C, and redissolved in methanol:pH 2.5 water (50:50, v:v) for further cleanup by solid-phase extraction (SPE) using methylene chloride. The resulting methylene chloride extracts are combined, rotary evaporated to dryness, and dissolved via sonication in distilled water. Imazamox is determined by HPLC on a C-8 reverse-phase column (5 μ Supelcosil LC-8-DB) using a mobile phase of acetonitrile:formic acid:water (20:1:79, v:v:v). The HPLC system is equipped with a UV detector set at 254 nm. Imazamox is quantitated by comparison of sample peak responses with those of an external reference standard. The limit of quantitation is 0.05 ppm. The method and concurrent recovery data indicate that the submitted HPLC/UV method for the determination of imazamox in soybean seed is adequate for data collection. Recoveries of imazamox were 70-110% from soybean seed fortified at 0.05-0.50 ppm.

M 2333: Methylene chloride extracts of soybean seed samples following GPC and solid-phase extraction (SPE) clean up and bearing positive (>0.05 ppm) residues of imazamox are injected onto a Whatman RAC II Partisil 5 ODS-3 LC column. A mobile phase of methanol:water (25:75, v:v) acidified with 0.5% trifluoroacetic acid is used. The mass spectrometer is operated in the selected ion monitoring mode, and the $(M+H)^+$ ion of imazamox at m/z 306^+ is monitored. This method was validated by fortifying samples of soybean seed with imazamox at 0.05 ppm. Apparent residues of imazamox were not quantifiable (<0.05 ppm) in/on two untreated samples of soybean seed. Recoveries of imazamox from soybean seed fortified at the limit of quantitation (0.05 ppm) were 76% and 79%. Representative mass chromatograms of standards, untreated soybean seed samples, and soybean seed samples fortified at 0.05 ppm were included. The validation data demonstrate that LC/MS Method M 2333 is satisfactory for the confirmation of imazamox residues quantifiable at ≥0.05 ppm in soybean seed.

Method M2248.01 has been successfully validated by Analytical Chemistry Branch (ACB)/Biological and Economic Analysis Division (BEAD) for residues of AC 299,2263 in soybean seeds at 0.05 ppm and 0.1 ppm levels. Method M 2248.01 is satisfactory for residue data collection and enforcement of a

tolerance for residues of imazamox *per se* in/on soybeans. Method M2333 has also been successfully validated by ACB/BEAD to confirm the presence of residues of AC 2992263 in soybean seeds at 0.05 ppm and 0.1 ppm levels.

iv. Storage Stability

American Cyanamid submitted data (MRID 43193239) depicting the frozen storage stability of residues of imazamox in/on soybean seed. Untreated samples of soybean seed were fortified with imazamox at 0.50 ppm and stored frozen at approximately -10 C for up to 12 months. Samples were extracted immediately after fortification and after 3, 6, and 12 months of frozen storage, and were analyzed within 2-3 days of extraction. Samples were analyzed using HPLC/UV method M 2248. The petitioner did not provide representative chromatograms or sample calculations.

Apparent residues of imazamox were not quantifiable (<0.05 ppm) in/on four unfortified samples of soybean seed. The submitted storage stability data indicate that residues of imazamox are stable under frozen storage conditions for up to 12 months in soybean seed.

American Cyanamid submitted additional data (MRID 43876232) which indicates imazamox is stable in soybean seeds for intervals up to 24 months. Stability of imazamox in soybean forage and hay is not germane at this time. Additional storage stability data are not required.

v. Magnitude of the Residue - Meat, Milk, Poultry & Eggs

No livestock feeding studies were submitted with this petition. Based upon information provided in the metabolism studies and comparison to the maximum dietary burden (0.017 - 0.025 ppm), there is no reasonable expectation of residues in meat, milk, poultry or eggs.

vi. Magnitude of the Residue - Crop Field Trials/ Processed Commodities

Crop Field Trials

The petitioner has submitted 24 field residue trials (MRIDs 43193239 & 43876232) and in each case, sample residues are reported as less than the limit of quantification (LOQ), less than 0.05 ppm. Geographic representation is adequate and together the test states account for 84% of the 1992 U.S. soybean production (*USDA Agricultural Statistics 1993*). Therefore, HED concludes that residues of imazamox are not likely to exceed 0.1 ppm, the proposed tolerance level, when imazamox is used on soybeans as provided in the current Directions for Use.

Processed Commodities

The requirement for a soybean processing study is waived, because residues of imazamox were not quantifiable in/on soybean seeds from crop field trials following treatment at 5x the proposed maximum single application rate. Data in the soybean metabolism study indicate that residues of imazamox do not concentrate in soybean oil.

Residue data on aspirated grain fractions are not required for the proposed use of imazamox on soybeans, because the use pattern is a prebloom application and because ^{14}C residues were not quantifiable (<0.01 ppm) in field treated soybean seed from 3.3 exaggerated application rate.

vii. Confined Rotational Crops

American Cyanamid submitted data (MRID 43193243) depicting the potential for accumulation of [6-pyridine-^{14}C]imazamox in rotational crops. The test material, [6-pyridine-^{14}C]imazamox (specific activity 100.15 μCi/mg, radiochemical purity 98.0%), was diluted with [6-pyridine-^{13}C]imazamox (as a mass marker) and non-radiolabeled imazamox, and formulated as the ammonium salt in aqueous solution. The specific activity of the treatment solution was 4.07 μCi/mg. The study indicates that ^{14}C-residues of imazamox did not accumulate (<0.01 ppm) in/on wheat commodities planted 100 days after [6-pyridine-^{14}C]imazamox was applied to soybeans in sandy loam soil at 1.6x the proposed maximum single application rate. At the 268-day rotation, radioactive residues were less than 0.01 ppm in/on radish, lettuce, and corn commodities. No characterization or identification of the residues is required.

Tolerances on rotational crops need not be established. No additional residue characterization or field rotational crop studies are required. No residues of concern were quantifiable in crops planted at 100-day or 268-day rotations. These data support the proposed 4-month plantback interval for barley, rye, and wheat, and the 9-month plantback interval for alfalfa, beans, corn, cotton, oats, peas, peanuts, potatoes, rice, sorghum (grain) and tobacco. Based on the submitted data, the 18-month plantback interval proposed for all other crops is not necessary and may be shortened to 9 months unless it is required for phytoxicity.

b. Dietary Exposure - Drinking Water

OPP's Environmental Fate and Effects Division (EFED) reviewed environmental fate data (requirements listed under 40 CFR §158.290) to support the registration of imazamox. Based on that review the following information was provided by EFED regarding drinking water exposure.

Imazamox is a member of the imidazolinone class of herbicides. The imidazolinones, as a class, have characteristics similar to compounds known to leach to ground water (mobile and persistent) and to runoff from the soil surface during periods of precipitation and/or irrigation. EFED notes that these chemicals have similar environmental fate properties as the sulfonylurea herbicides (e.g., low application rates, mobility). However, imazamox does differ from the other imidazolinone pesticides in that it degrades aerobically (half-life 27 days); most imidazolinones are more persistent. Since imazamox degrades via aqueous photolysis and aerobic metabolism it is considered somewhat persistent in the field.

i. Ground Water

Imazamox will be mobile on many soils however the limited persistence will restrict much of it from reaching ground water. Although imazamox does exceed several of the criteria for restricted use, because of its limited persistence, the Environmental Fate and Effects Division (EFED) *does not* consider imazamox to be a candidate for restricted use due to ground water concerns.

ii. Surface Water

Imazamox should not persist in shallow surface waters. However, it should persist in water at greater depths when an anaerobic environment exists and where photolytic degradation is not a factor. EFED calculated Estimated Environmental Concentrations's (EEC's) using the Generic Expected Environmental Concentration Program (GENEEC) to estimate exposure from surface water for use of imazamox on celery, lettuce, and endive.

The GENEEC program uses a few basic chemical parameters and pesticide label application information to provide a rough estimate of the expected environmental concentrations. The model calculates the concentration of pesticide in a hypothetical 1-ha, 2-m deep pond taking into account adsorption to soil and sediment, soil incorporation, degradation in soil before runoff to a water body, and degradation within the water body. The model also accounts for direct deposition of spray drift into the water body. The rate of spray drift deposition is assumed to be 1% and 5% of the application rate for ground and aerial applications, respectively.

Only a single experimentally determined value, with the exception of the Koc, was available for each input parameter used in the GENEEC Program. Since there was no correlation between the organic carbon content and adsorption, the Koc (143) for a clay loam (soil GENEEC based on) was used. The input values were:

Soil Organic Carbon Partitioning Coefficient:	143.0
Soil Aerobic Metabolic Half-life:	27 days
Aquatic Aerobic Metabolic Half-life:	stable
Hydrolysis Half-life:	stable
Photolysis Half-life (at pH 7):	0.3 days
Water Solubility:	4500 ppm

Based on the GENEEC Program, the recommended chemical concentration value for use in human health risk assessments for surface water is 1 μg/L for chronic drinking water exposure. Using this exposure number the dietary exposure calculation for surface drinking water are as follows:

U.S. Population Exposure = (chemical concentration in μg/L in consumed water) (10^{-6}) (19.4 g/kg body wt/day) = mg/kg/day

Non-nursing Infants Exposure = (chemical concentration in μg/L in consumed water) (10^{-6}) (35.3 g/kg body wt/day) = mg/kg/day

Children (1-6) Exposure = (chemical concentration in μg/L in consumed water) (10^{-6}) (37.1 g/kg body wt/day) = mg/kg/day

The 10^{-6} represents a conversion factor for:

$$\frac{(L)\ (ml\ H2O)\ (mg)}{(10^3\ ml)\ (g\ H2O)\ (10^3\ \mu g)}.$$

The 19.4, 35.3 and 37.1 are estimates of the median drinking water intake for the United States and selected subpopulations. The numbers were derived from self reported body weights and water consumption values reported in USDA's 1977-1978 survey.[1]

Subgroup	Chemical Concentration (μg/L)	Exposure to Imazamox from Drinking Water (Surface Water) mg/kg/day
U.S. Population	1	2×10^{-5}
Non-nursing Infants	1	4×10^{-5}
Children	1	4×10^{-5}

[1] Information taken from a paper by A.G. Ershow and K.P. Cantor, *Total Water and Tapwater Intake in the United States: Population based Estimates of Quantities and Sources.*

c. Dietary Risk Characterization

i. Acute Dietary

As part of the hazard assessment process, the TES Committee reviews the available toxicological database to determine if there are toxicological endpoints of concern (refer to the Toxicological Endpoints for Risk Assessment section above). For imazamox, the Agency does not have a concern for acute dietary exposure since the available data do not indicate any evidence of significant toxicity from a one day or single event exposure by the oral route. Therefore, an acute dietary risk assessment is not required for imazamox at this time.

ii. Chronic Dietary Risk

A chronic dietary risk assessment is required for imazamox. The RfD used for the chronic dietary analysis is 3.0 mg/kg bwt/day. A tolerance of 0.1 ppm in/on soybeans was used. Since imazamox is a new chemical, no tolerances for imazamox have been established previously. A chronic exposure analysis was performed using tolerance level residues and 100 percent crop treated information to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and 22 subgroups.

The chronic analysis showed that exposure from the proposed tolerance, for use of imazamox in/on soybeans, for the general population and all 22 subgroups would be less than 1% of the RfD. This chronic analysis for imazamox is an upper-bound estimate of dietary (food) exposure with all residues at tolerance level and 100 percent of the commodities assumed to be treated with imazamox. Therefore, even without refinements, the chronic dietary (food) risk due to exposure from imazamox appears to be minimal for this petition on soybeans, and does not exceed the RfD for the general population or any of the 22 subgroups.

iii. Aggregate Chronic Dietary/Drinking Water Risk

The chronic drinking water risk is calculated as a percent of the RfD taken up by drinking water. The following calculation is used:

%RfD = (Exposure from Water mg/kg/day) ÷ (RfD mg/kg/day) x 100

In order to determine the percent of the RfD taken up by drinking water for use of imazamox in/on soybeans the exposure estimates are taken from the Dietary Exposure - Drinking Water section above and the RfD of 3.0 mg/kg/day is used. The chronic analysis showed that chronic exposure from drinking water to both the U.S. population and children would be less than 1% of the RfD. Therefore, the combined exposure of chronic dietary (food and drinking water) to imazamox would be no greater than 1% of

the RfD for both the U.S. population and children

The drinking water values were developed for use in eco-risk assessment and represent a reasonable upper-bound estimate for eco-risk assessment. It is expected they represent an overestimate for human health risk assessments. The chronic dietary analysis is also an upper-bound estimate of dietary exposure with all residues at tolerance level and 100 percent of the commodity assumed to be treated with imazamox. Therefore, even without refinements, HED does not consider the combined aggregate chronic dietary/drinking water risk to exceed the level of concern.

4. OCCUPATIONAL AND RESIDENTIAL EXPOSURE AND RISK CHARACTERIZATION

As part of the hazard assessment process, the TES Committee reviews the available toxicological database to determine if there are toxicological endpoints of concern (refer to the Toxicological Endpoints for Risk Assessment section above). For imazamox, HED does not have a concern for short-term, intermediate-term, or chronic-term occupational or residential exposure since the available toxicology data indicates minimal toxicity only at a very high dose, such as the limit dose by the dermal or inhalation routes. Therefore, occupational or residential risk assessments are not required for imazamox at this time.

5. CUMULATIVE EFFECTS

Section 408 of FQPA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." While the Agency has some information in its files that may be helpful in determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodology to resolve the scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will enable it to develop and apply policies for evaluating the cumulative effects of chemicals having a common mechanism of toxicity. At present, however, the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments.

In the case of imazamox, HED has not yet determined whether or how to include this chemical in a cumulative risk assessment. This tolerance determination therefore does not take into account common mechanism issues. After EPA develops a methodology for

applying common mechanism of toxicity issues to risk assessments, the Agency will develop a process (either as part of the periodic review of pesticides or otherwise) to reexamine those tolerance decisions made earlier.

On this basis, the registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether imazamox share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for imazamox need to be modified or revoked.

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